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Tetrahedron Letters 47 (2006) 5251–5253
Tetrahedron Letters

Total synthesis of (±)-pentenomycin

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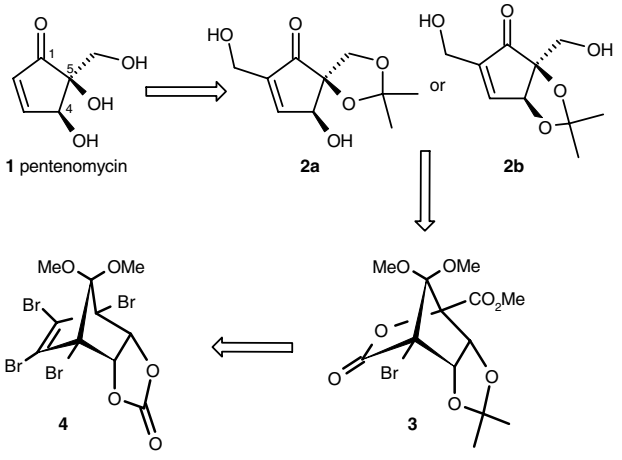
Received 21 April 2006; revised 15 May 2006; accepted 24 May 2006
Available online 12 June 2006

Abstract—A concise stereoselective route to (±)-pentenomycin **1** in 33% overall yield starting from the readily accessible Diels–Alder adduct **4** is reported. The key reaction involves decarbonylation of β-methoxy-α,β-unsaturated aldehyde **8** obtained from β-hydroxy-dimethylketal **6**.

Ever since the isolation of pentenomycin I **1**,[1] usually referred to as pentenomycin, belonging to the biologically active family of closely related polyhydroxylated cyclopentenoid antibiotic natural products was reported, several total syntheses have appeared in the literature.[2–4] Pentenomycin exhibits moderate activity against Gram-positive and Gram-negative bacteria. The presence of a cyclopentenone moiety in pentenomycins attracted considerable attention due to its occurrence in a diverse range of biologically potent natural products and a multitude of structurally complex pharmacologically important agents.[2] The synthetic approaches to pentenomycin can be categorized as racemic[3] and enantiopure syntheses.[4,5] The latter can be further classified as (i) those involving carbohydrate-based starting materials[4] and (ii) asymmetric synthesis.[5]

Recently, we reported a short and stereoselective synthesis of 2-hydroxymethyl-4-deoxypentenomycin and 2-hydroxymethylpentenomycin derivatives.[6] Our strategy was based on the establishment of the C-5 tertiary center as well as the C-4 stereocenter at an early stage in a stereoselective manner as depicted in Scheme 1. Hydroxymethyl functional group addition to pentenomycin **1** at C-2 allowed us to simplify the target to the bridged-lactone **3**, which is easily available from the Diels–Alder adduct **4** via the methods developed in our laboratory.[7] Indeed the 2-hydroxymethylpentenomycin derivatives **2** were synthesized in 38% overall yield from **4**. The advantage gained by the functional group addition at C-2 that facilitated realization of **4** as a convenient starting material was offset by the difficulty encountered in its removal in **2** through an originally planned oxidation–decarboxylation protocol, perhaps due to the sensitivity of the enone moiety in these systems. We now report an elegant solution to this problem that led us to accomplish the total synthesis of the title compound in high overall yield.



Scheme 1. Retrosynthetic strategy for pentenomycin.

Our initial efforts toward the one-carbon scission of **2** to obtain **1** met with failure. We then took recourse to the intermediate **5**, which had furnished **2** upon treatment with Amberlyst-15 in acetone,[6] and protected the vicinal diol to obtain the bis-acetonide derivative **6** (Scheme 2). Oxidation of the hydroxymethyl moiety using $RuCl_3$–$NaIO_4$ furnished the carboxylic acid derivative **7** in 70% yield. We anticipated that under hydrolytic

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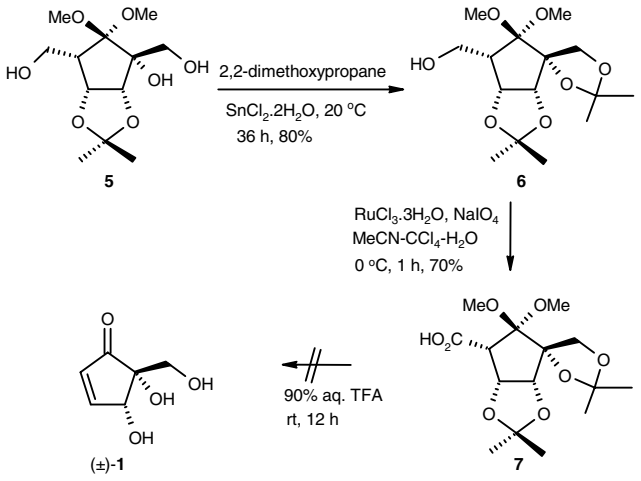
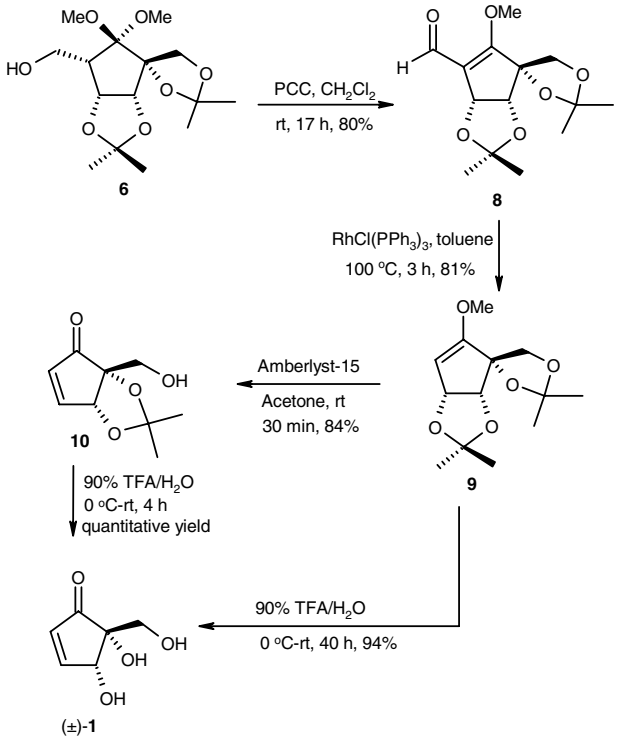
doi:10.1016/j.tetlet.2006.05.156



Scheme 2.

conditions, in addition to the events described during the hydrolysis of **5** (deprotection of the dimethyl acetal followed by elimination of the hydroxy functionality with reorganization of the acetonide protection),[6] decarboxylation would also takes place giving pentenomycin. Unfortunately, a complex mixture of products was observed when **7** was treated with 90% aqueous TFA (Scheme 2).

We modified the strategy for the one-carbon scission and subjected the bis-acetonide derivative **6** to PCC oxidation (Scheme 3). To our surprise, β-methoxy-α,β-unsaturated aldehyde **8** was obtained in 80% yield. The formation of this unexpected product may be accounted for via the elimination of one of the methoxy



Scheme 3.

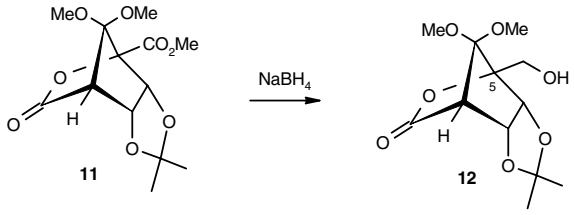
groups of the β-ketal under acidic reaction conditions. Aldehyde **8** was subjected to Wilkinson's rhodium complex [$RhCl(PPh_3)_3$] in toluene at 100 °C to afford the corresponding decarbonylated product **9** in 81% yield.[8]

With the acquisition of one-carbon scission product **9**, the stage was set for the final step where hydrolysis of the enol ether and two acetonide moieties with concurrent elimination of the C-3 hydroxy group would lead to pentenomycin. Hydrolysis was carried out initially employing Amberlyst-15 in moist acetone which furnished **10**, still possessing one acetonide group that was now located between the C-4,5 hydroxyl groups. Subjecting **10** to 90% aqueous TFA furnished (±)-pentenomycin in quantitative yield. Alternatively, treatment of **9** with 90% aqueous TFA directly led to (±)-pentenomycin in 94% yield (Scheme 3).[9]

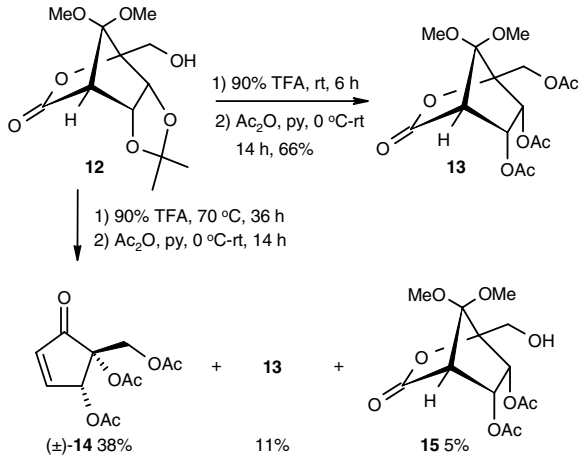
Having achieved the synthesis of pentenomycin via a strategy based on decarbonylation of aldehyde **8**, we next focused our attention on bridged-lactone intermediate **11**. This compound was obtained by tributyltin hydride mediated hydrodebromination of **3** in high yield.[6] We had reported previously, in a related system, that the methyl ester moiety, rather than the lactone which is generally considered more reactive, is reduced chemoselectively by $NaBH_4$ in THF to the corresponding alcohol.[7] When bridged-lactone **11** was treated with 2.5 equiv of $NaBH_4$ in THF at room temperature, the reaction was sluggish and furnished 85% of the corresponding alcohol **12** in 7 days (Table 1). This could perhaps be attributed to the steric congestion due to the presence of an α-*endo*-hydroxyl carrying acetonide protection. Heating the reaction to reflux gave a complex mixture. In order to reduce the reaction time and to improve the yield of **12**, the use of solvents, such as MeOH, diglyme, and dioxane, were investigated (Table 1). The optimum result was obtained with 1.5 equiv of $NaBH_4$ in dioxane at 85 °C. The reaction was complete in 1 h, giving 95% of **12** (Table 1, entry 5).

A close inspection of alcohol **12** revealed that not only the C-5 tertiary center, but also the C-2 substituent were in the correct oxidation state to allow one-carbon scission via decarboxylation under hydrolytic conditions. Therefore, we thought that subjecting **12** to acidic hydrolysis might directly lead to pentenomycin via dimethyl ketal hydrolysis (C-1), decarboxylation (C-2), and hydroxy group (C-3) elimination in one-pot. With this in mind, **12** was treated with 90% aqueous TFA at room temperature for 6 h, followed by acetylation of the crude reaction mixture after removal of TFA under vacuum. The product obtained was characterized as triacetate **13** (Scheme 4). To our delight, when the temperature for the hydrolysis step was raised to 70 °C and the reaction was allowed to stir for 36 h, 38% of pentenomycin triacetate **14**[9] along with 11% of **13** and 5% of diacetate **15** were obtained. Although the yield of pentenomycin triacetate **14** obtained in this way was low and fluctuated due to the sensitivity of the enone moiety under the harsh reaction conditions, it is remarkable that **12** could indeed furnish the target molecule in a one-pot operation.

Table 1. $NaBH_4$ reduction of **11**



Entry	Solvent	Temp	Time	Equiv of $NaBH_4$	Isolated yield (%)
1	THF	rt	7 d	2.5	85
2	THF	Reflux	1 h	2.0	Intractable mixture
3	MeOH	Reflux	3 h	2.0	56
4	Diglyme	90 °C	4 h	1.5	72
5	Dioxane	85 °C	1 h	1.5	95



Scheme 4.

In conclusion, we have demonstrated a concise stereoselective route to (±)-pentenomycin in 49% overall yield starting from **5**, which in turn was obtained from the readily accessible Diels–Alder adduct **4** in 68% overall yield. An interesting observation during the PCC oxidation of β-hydroxy-dimethylketal **6** leading to β-methoxy-α,β-unsaturated aldehyde **8** was reported. A highly efficient chemoselective reduction of the ester moiety in lactone **11**, followed by a one-pot transformation of the resulting alcohol **12** to (±)-pentenomycin triacetate **14**, was also reported.

Acknowledgements

Financial support from the Department of Science and Technology (DST), New Delhi, is gratefully acknowledged. F.A.K. acknowledges the DST for a Swarnajayanti Fellowship. We thank Mr. T. Ogino of Mitsui Fine Chemicals, Inc., Tokyo, Japan, for a generous gift of vinylene carbonate.

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9. The spectral data (^1H and ^{13}C) of both (±)-pentenomycin **1** and (±)-pentenomycin triacetate **14** were in agreement with the reported values.[1]